

## REMARKS

### The Invention

The invention is based on the discovery that homozygous securin-defective cells fail to separate their metaphase chromosomes appropriately, and thus exhibit aneuploidy. The invention is drawn to an isolated and purified homozygous securin-defective human cell line. (Claim 1.) The invention is also drawn to a pair of isogenic mammalian cell lines. A first cell line is homozygous securin-defective and a second cell lines is securin-proficient. (Claim 5.) The invention is also drawn to a method of screening compounds to identify potential anti-cancer agents. A test compound is contacted with a first mammalian cell line which is homozygous securin-defective and a second cell line which is securin-proficient. A test compound is identified as a potential anti-cancer agent if it preferentially inhibits growth of the first cell line relative to the second cell line. (Claim 10.)

### The Amendments

Claim 5 has been amended to recite “[a] pair of isogenic mammalian cell lines” in place of “[a] pair of isogenic cell lines.” The amendment is supported by the specification which discloses, “Any type of mammalian cell that can be maintained in culture or in an animal and can be transfected can be used to generate a securin gene-defective cell.” (Page 10, lines 13-15.) Thus this amendment is supported by the specification and adds no new matter to the claims.

Claims 11-15 have been amended to recite that “a test compound is identified as a potential anticancer agent if it inhibits growth of the first cell line at least 2, 5, 10, 20, or 50 fold more than the second cell line” in place of the recitation “the ratio of inhibition is at least 2:1, 5:1, 10:1, 20:1, or 50:1, respectively.” The amendment clarifies by providing proper antecedent

basis in claim 10. Thus the amendment merely clarifies the claims and does not narrow the scope of the claims or add new matter.

New claims 19-23 are dependent on originally filed claims 5-8, and 10, respectively. They each recite that the isogenic cell lines are “human cell lines.” The specification supports this amendment where it discloses that the cells can be from any mammal, “preferably human tumor, more preferably human colon tumor cells.” (Page 10, lines 22-23.) Claim 1 also recites a homozygous securin-defective human cell line. Thus the new claims are supported by the application and add no new matter to the claims.

#### The Rejection of Claims 11-15 Under 35 U.S.C. § 112

Claims 11-15 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. Applicants respectfully traverse.

“To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that the ‘inventor invented the claimed invention.’” *The Regents of the University of California v. Eli Lilly and Company*, 19 F.3d 1559, 1566 (Fed. Cir. 1997), emphasis added, citing *Lockwood v. American Airlines, Inc.* 107 F.3d 1565, 1572 (Fed. Cir. 1997); and *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989).

Rejected claims 11-15 are drawn to methods of screening compounds to identify potential anti-cancer agents. The methods recite that the potential anti-cancer agent preferentially inhibits growth of a first cell line at least 2-fold (claim 11), 5-fold (claim 12), 10-fold (claim 13), 20-fold

(claim 14), or 50-fold (claim 15) relative to a second cell line. The patent specification describes rejected method claims 11-15 in sufficient detail such that one skilled in the art would conclude that applicants invented the methods of these claims.

The Office Action asserts, however, that the claims are not described because “the instant specification provides no description of a compound or compounds which can actually inhibit the growth of a securin defective cell line relative to the securin-proficient cell line at the levels claimed.” (Paper 7, page 2, line 26 to page 3, line 1.) The claimed invention is not, however, drawn to compounds *per se*. The claimed invention is drawn to methods of identifying these compounds. Claims 11-15 merely set forth threshold levels for determining preferential inhibition in the methods. The specification need not describe specific compounds which meet these threshold levels because the claimed invention is the method, not the compound.

The specification must describe the methods for identifying the compounds. The claimed invention can be described by “such descriptive means as words, structures, figures, diagrams, formulas, etc.” *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572 (Fed. Cir. 1997). Applicants describe the invention of claims 11-15 by providing such descriptive means.

The specification describes all steps of the claimed methods. The method comprises contacting a test compound with a first cell line that is homozygous securin-defective and a second cell line that is securin-proficient.” The specification describes this step where it discloses, “A test compound is contacted with each of the two isogenic cell lines.” (Page 4, lines 21-22.) The specification also describes potential test compounds that can be screened in the methods. The specification discloses, “Potential therapeutic agents which can be tested include agents which are known in the art to have pharmacological activity or can be compounds whose pharmacologic activity is unknown.” (Page 9, lines 5-7.) Specific sources from which the

compounds can be isolated and example compounds that can be screened are also disclosed.

(Page 9, lines 7-16.)

The methods of claims 11-15 also comprise a step of “identifying as a potential anticancer agent a test compound which preferentially inhibits growth of the first cell line relative to the second compound.” The specification also conveys that applicants invented this step of the methods.

The ratio of inhibition or killing can be determined by any means known in the art. It is well known in the art that viable cells exclude dye. Viable cells can be observed to have an intact membrane and do not stain, where as dying or dead cells have “leaky” membranes and do stain. Any dyes known in the art can be used, such as, for example, trypan blue, eosin Y, naphthalene black, nigrosin, erythrosine B, and fast green. The ratio of killed or growth-inhibited homozygous securin-defective cells:securin-proficient cells can also be determined by incorporation of labeled metabolites, such as, for example, 3H-thymidine. Cells can be cultured in medium containing radiolabeled metabolites; uptake or incorporation of the metabolites indicates cells growth.

Page 7, lines 3-11.

Moreover, the specification describes that compounds are identified as anti-cancer agents if they preferentially inhibit growth of homozygous securin-defective vs. securin-proficient cells lines at the recited differential levels of inhibition. The specification discloses, “Preferably the agents selected as potential therapeutic agents will kill or growth-inhibit securin-defective cells relative to securin-proficient cells in at least a 2:1, 5:1, 10:1, 20:1, or 50:1 ratio.” (Page 9, line 23-24.) One of skill in the art would recognize from the disclosure of the application that applicants invented the invention of claims 11-15 because they adequately describe all aspects of the claimed methods. Withdrawal of this rejection to claims 11-15 is respectfully requested.

The Rejection of Claims 1-10, 16, and 18 Under 35 U.S.C. § 103(a)

Claims 1-10, 16, and 18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Morales (Oncogene, 2000, vol. 19, pp. 403-409) and Zur et al. (EMBO, 2001 Feb 15, vol. 20, pp. 792-801) in view of Lengauer et al. (Nature, 1998, vol. 396, pp. 643-649). Applicants respectfully traverse.

To reject claims under 35 U.S.C. § 103(a), the Patent Office has the burden of establishing a *prima facie* case of obviousness. To establish *prima facie* obviousness of a claimed invention there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. MPEP 2143.01, citing *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992). It is respectfully submitted that there is no motivation to combine Morales and Zur with Lengauer to arrive at the invention of claims 1-10, 16, and 18. Thus the *prima facie* case of obviousness fails.

Each of the rejected claims employs a homozygous securin-defective cell line. Claims 1-4 are drawn to an isolated and purified homozygous securin-defective human cell line. Claims 5-9 are drawn to a pair of isogenic mammalian cell lines in which a first cell line is homozygous securin-defective and a second cell line is securin-proficient. Claims 10, 16, and 18 are drawn to a method of screening compounds to identify potential anti-cancer agents using a pair of isogenic mammalian cell lines in which a first cell line is homozygous securin-defective and a second cell line is securin-proficient. One of skill in the art would not have been motivated to combine Morales, Zur, and Lengauer to arrive at the homozygous securin-defective cells recited in the rejected claims.

Morales teaches an analysis of the human securin gene. The Patent Office cites Morales

as “agree[ing] with the prior art which postulates that defective Securin results in aneuploidy which contributes to the tumorigenic phenotype.” (Paper 7, page 4, lines 6-8, citing page 407, sentence spanning columns 1 and 2.) However, neither Morales, nor the prior art, teaches that defective securin results in aneuploidy. Morales agrees with the prior art that wild-type securin inhibits sister-chromatid separation. Morales states, “During the revision of this manuscript, Zou et al. (1999) reported that PTTG encodes a securin, a protein which inhibits sister-chromatid separation by binding to separin. Our results are in total agreement with this function of hPTTG.” (Page 407, sentence spanning column 1 and column 2.) Thus Morales does not teach any phenotype of defective securin. Morales also does not teach that defective securin contributes to the tumorigenic phenotype. Morales teaches, “On the basis of its function as a securin, Zou et al. (1999) propose that PTTG tumorigenic activity is the result of aneuploidy caused by defects in the sister-chromatid separation.” (Page 407, second column, lines 11-14.) Thus Morales teaches that wild-type securin contributes to both aneuploidy and the tumorigenic phenotype.

Zur studied ubiquitination and degradation patterns of securin by introducing a non-degradable mutant securin into cell lines. The Patent Office cites Zur as teaching that “a cell line overexpressing a double mutant Securin were [sic] defective in chromatid separation.” (Paper 7, page 4, lines 12-13.) Zur teaches that the defect is due to overexpression rather than defective function: “Both wild-type and mutant securins precipitated equal amounts of separin, showing that the mutations did not affect the capacity of securin to bind separin. (Page 798, column 1, lines 12-15.) Zur also teaches that cells overexpressing wild-type securin would be expected to have the same phenotype as cells expressing the non-degradable securin variant:

The non-degradable variant of securin leads to a high degree of genetic instability and unequal separation of chromatin to daughter

cells. The incomplete separation could also lead to chromosome breakage due to the pulling force of the spindle and of the dividing cells. It is easy to imagine that overexpression of the wild-type variant could have a similar effect, even though at a lower rate.

Page 799, second column, lines 8-15. Thus, Zur teaches that wild type securin is expected to cause genetic instability if overexpressed in cells.

Lengauer teaches that there are different genetic instabilities that play a role in cancers, such as chromosomal instability (CIN) and microsatellite instability (MIN). Lengauer also teaches criteria for identifying genes that contribute to CIN. The Patent Office cites Lengauer as teaching that “in order to test if a specific gene is responsible for chromosomal instability it is necessary to have in hand an immortalized cell line in which the targeted gene has been deleted.” (Paper 7, page 4, lines 20-22.)

The Office Action asserts that it would have been obvious to make securin-defective cells because Morales and Zur teach that securin is involved in chromosomal instability. However, rather than teaching that knocking out securin causes CIN phenotype, Morales and Zur each teach that overexpression of wild-type securin leads to the tumorigenic, CIN phenotype. Morales teaches, “Failure to normally regulate hPTTG [securin] level could lead to the uncontrolled proliferation that is a hallmark of cancer, and could explain the *in vitro* and *in vivo* transforming abilities of *hpttg*.” (Page 407, column 2, lines 8-11.) Thus Morales teaches that wild-type securin, *hpttg*, leads to the cell proliferation that is characteristic of cancer. Zur teaches that securin is an oncogene referring to the “tumor-promoting activity of securin/PTTG.” (Page 799, second column, lines 7-8.)

One of ordinary skill in the art would not have considered knocking out a gene to cause a phenotype already demonstrated by overexpression of the wild-type gene. Morales and Zur taught that securin is an oncogene which causes incomplete chromosomal separation. To

recapitulate the tumorigenic CIN phenotype of securin, as suggested by Lengauer, one of skill in the art would have overexpressed securin based on the teachings of Morales and Zur. Thus one of skill in the art would not have been motivated to combine Morales and Zur with Lengauer which would have led to knocking out the gene apparently responsible for the desired phenotype.

Even if, *arguendo*, the Patent Office maintains that one of skill in the art would be motivated to combine Morales and Zur with Lengauer to arrive at the claimed invention, unexpected results rebut the rejection. The homozygous, securin-defective, mammalian cell lines surprisingly have properties contrary to those predicted on the basis of Morales and Zur.

Both Morales and Zur teach that wild-type securin inhibits chromatid separation leading to aneuploidy or genetic instability and that wild-type securin is oncogenic. Morales teaches that securin is “a protein which inhibits sister-chromatid separation by binding to separin” (page 407, sentence bridging columns 1 and 2) and that securin may be tumorigenic as a “result of aneuploidy caused by defects in the sister-chromatid separation” (page 407, second column, lines 13-14). Morales also teaches, “Failure to normally regulate hPTTG level could lead to the uncontrolled proliferation that is a hallmark of cancer, and could explain the *in vitro* and *in vivo* transforming abilities of *hpttg*.” (Page 407, column 2, lines 8-11.) Zur teaches, “The non-degradable variant of securin leads to a high degree of genetic instability and unequal separation of chromatin to daughter cells. [...] It is easy to imagine that overexpression of the wild-type variant could have a similar effect, even though at a lower rate.” (Page 799, second column, lines 8-15.) Zur also refers to the “tumor-promoting activity of securin/PTTG.” (Page 799, second column, lines 7-8.) Thus Morales and Zur indicate that overexpression of wild-type securin leads to aneuploidy or genetic instability, and that overexpression of wild-type securin leads to oncogenesis.



A homozygous securin-defective cell line would therefore not have been expected to have the chromosomal instability phenotype, as does the wild-type over-expressing cell line. Rather, a securin-defective cell line would have been expected to have the opposite phenotype and possibly to have been lethal.<sup>1</sup>

Withdrawal of this rejection of claims 1-10, 16 and 18 is respectfully requested as a *prima facie* case has not been made. If a *prima facie* case is held to be properly made, the unexpected results demonstrated in the specification rebut them.

#### The Rejection of Claims 1-10, and 16-18 Under 35 U.S.C. § 103(a)

Claims 1-10 and 16-18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Morales (Oncogene, 2000, vol. 19, pp. 403-409) and Zur et al. (EMBO, 2001 Feb 15, vol. 20, pp. 792-801) in view of Lengauer et al. (Nature, 1998, vol. 396, pp. 643-649) and in further view of Fiebig (Human Tumor Xenographs in Anticancer Drug Development, 1988). Applicants respectfully traverse.

Claim 17 is the only claim in this obviousness rejection that was not previously rejected over Morales, Zur and Lengauer. Claim 17 recites that the cell lines used in the method of screening compounds are in xenografts.

To reject claims as *prima facie* obvious there must be some motivation to combine the asserted references to arrive at the claimed invention. Morales, Zur, Lengauer, and Fiebig would not have been combined by one of skill in the art to arrive at the claimed invention.

As indicated above Morales, Zur, and Lengauer would not have been combined to arrive at an isolated and purified homozygous securin-defective human cell line, a pair of isogenic

---

<sup>1</sup> The specification discloses that loss of securin is lethal in fission yeast. (Page 3, line 22, citing Funabiki *et al.* 1996, EMBO J. 15:6617-28.)

mammalian cell lines in which a first cell line is homozygous securin-defective and a second cell line is securin-proficient, or a method of screening compounds to identify potential anti-cancer agents using a pair of isogenic mammalian cell lines in which a first cell line is homozygous securin-defective and a second cell line is securin-proficient. Morales and Zur teach that wild-type securin inhibits chromatid separation and is oncogenic. Morales teaches, "Failure to normally regulate hPTTG level could lead to the uncontrolled proliferation that is a hallmark of cancer, and could explain the *in vitro* and *in vivo* transforming abilities of *hpttg*." (Page 407, column 2, lines 8-11.) Thus Morales teaches that securin, *hpttg*, leads to the cell proliferation that is characteristic of cancer. Zur teaches that securin is an oncogene, referring to the "tumor-promoting activity of securin/PTTG." (Page 799, second column, lines 7-8.) Lengauer teaches that genes suspected of contributing to chromosomal instability can be identified by "recapitulation of the CIN phenotype." (Page 647, second column, lines 9-10.) To recapitulate the CIN phenotype of securin, as suggested by Lengauer, one of skill in the art would have overexpressed securin based on the teachings of Morales and Zur.

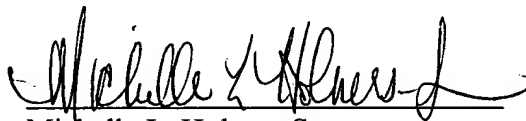
Fieberg provides no additional teaching that would motivate one of skill in the art to arrive at the homozygous securin-defective cell line of the claimed invention. Fieberg teaches a xenograft system as "a predictive assay for the individual treatment of patients and, furthermore, to validate the potential of human tumor-nude mouse system for testing new drugs." (Page 29, second column, lines 6-9.) Fieberg does not teach any gene, including securin, that is potentially involved in tumor formation. Fieberg also does not teach cell lines that are defective for particular genes or the utility of producing such cell lines. Fieberg teaches that the cells of "human tumors [were transplanted] subcutaneously into nude mice." (Page 25, second column, line 29.)

Thus none of Morales, Zur, Lengauer, or Fieberg provides any teaching that would have motivated one of skill in the art to combine the teachings to arrive at the homozygous securin-defective cell lines of the claimed invention. Withdrawal of this rejection to claims 1-10, and 16-18 is respectfully requested. The *prima facie* case of obviousness is defective.

Respectfully submitted,

Date: May 13, 2002

By:



Michelle L. Holmes-Son  
Registration No. 47,660

BANNER & WITCOFF, LTD.  
Eleventh Floor  
1001 G Street, N.W.  
Washington, D.C. 20001  
(202) 508-9100

## **Appendix I. Marked-Up Version of the Claims to Show Changes Made**

5. (Amended) A pair of isogenic mammalian cell lines in which a first cell line is homozygous securin-defective and a second cell line is securin-proficient.

11. (Amended) The method of claim 10 wherein a test compound is identified as a potential anti-cancer agent if it inhibits growth of the first cell line at least 2-fold more than the second cell line [the ratio of inhibition is at least 2:1].

12. (Amended) The method of claim 10 wherein a test compound is identified as a potential anti-cancer agent if it inhibits growth of the first cell line at least 5-fold more than the second cell line [the ratio of inhibition is at least 5:1].

13. (Amended) The method of claim 10 wherein a test compound is identified as a potential anti-cancer agent if it inhibits growth of the first cell line at least 10-fold more than the second cell line [the ratio of inhibition is at least 10:1].

14. (Amended) The method of claim 10 wherein a test compound is identified as a potential anti-cancer agent if it inhibits growth of the first cell line at least 20-fold more than the second cell line [the ratio of inhibition is at least 20:1].

15. (Amended) The method of claim 10 wherein a test compound is identified as a potential anti-cancer agent if it inhibits growth of the first cell line at least 50-fold more than the second cell line [the ratio of inhibition is at least 50:1].